TBI/TISSUE BANKS INTERNATIONAL

A Non-Profit, Non-Governmental Eye and Tissue Bunking Network

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97N-4845

December 23, 1999

Docket Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

Re: 21 CFR Parts 210, 211, 820 and 1271
[Docket No. 97N – 484S]

Proposed Rule: Suitability Determination for Donors of Human Cellular and Tissue-Based Products

Dear Sir or Madame:

Tissue Banks International (TBI) has commented on the FDA's "proposed approach document" and "proposed registration rule" whereby TBI communicated our objection to a comprehensive regulatory system for all tissue based products. Unlike the December 1993 Interim Final Rule where there was concern about unsafe imported tissue and potentially inadequate donor screening, the FDA's proposed new system of regulation for human cellular and tissue based products is not accompanied by a demonstrated need for additional regulation. Similarly, the proposed rule cited above is not based on a demonstrated need to modify the screening and testing regulations ffor the human allograft tissue currently regulated under the FDA's "tissue final rule".

TBI's objection to the current proposed rule is consistent with our previously communicated objections. There is mention of "concern" about communicable disease in the FDA commentary. To our knowledge, under the current regulation there have been no problems with transmission of communicable disease through the use of human tissue for the diseases currently listed or for those proposed to be added. The eye and tissue banking community has not been informed of the FDA's safety and effectiveness concerns.

Additionally, the FDA has not yet addressed the concerns expressed by TBI and many others in the eye and tissue banking community over the definition, specific interpretation and scope of certain concepts within the "proposed approach document" such as "homologous use", "minimal manipulation" and "systemic effect". The current proposed rule only

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increases to these concerns by adding the concept of "relevant communicable disease agents and disease". Unlike other areas regulated by the FDA such as drugs and medical devices, there is no formal mechanism in place or communication process whereby the FDA can receive input from the eye and tissue community on these concepts except by the rule making process. TBI believes the rule making process is not an effective method to obtain information, opinion and data on such concepts and has the potential for significant impact on our vital health care services.

Until such time as the issues mentioned above can be adequately addressed, TBI objects to the proposed changes to the "'tissue final rule" for human allograft tissue provided for transplantation except for the "proposed registration rule" which TBI supports. Excluded from the scope of TBI's comments are reproductive tissues or leukocyte-rich cells or tissues and tissues not previously regulated by the FDA. Additionally, TBI offers further comment in response to FDA's request for specific comments on the proposed rule and other relevant areas:

USE OF THE TERMS "MANUFACTURE" AND "PRODUCT": Use of these terms in the definitions and throughout the proposed regulation is objectionable for two reasons. First, these terms are not consistent with terms used in the tissue and eye banking field and in some cases, such as cornea1 tissue, are inaccurate. Second, most States have laws that specifically define the provision of human tissue for human transplant to be a service that does not constitute the sale of goods or products to which implied warranties apply. The language used in the proposed regulations appears to conflict with State law.

STEM CELLS & LEUKOCYTE-RICH TISSUE: The agency requested comment on the term '"leukocyte-rich". While TBI does not offer comment the term "leukocyte-rich', we do find the term "stem cells" insufficient to apply to cornea1 epithelial stem cells. Cornea1 epithelial stem cells are not leukocyte-rich. One suggestion being offered by the Eye Bank Association of America is to use a more precise term such as "hemotologic stem cells".

RELEVANT COMMUNICABLE DISEASE RISK AND DISEASE: The FDA is broadening its oversight from the screening and testing for HIV and Hepatitis in the "tissue final rule" to all "relevant communicable disease risk and disease" in the current proposed rule. A relevant communicable disease risk and disease as stated in the proposed rule is 1) sufficiently prevalent among potential donors to warrant screening or testing of all donors; 2) for which there is a risk of transmission by a human cellular or tissue-based product.. . 3) that pose significant health risk as measured by morbidity and mortality; and 4) for which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved or cleared for such use by FDA and is available.

The FDA already deemed relevant TSE/CJD and treponema pallidum in addition to HIV and hepatitis (for non leukocyte-rich tissue) contained in the "'tissue final rule" requiring screening for former and testing for the later. The tissue and eye banking community already screens for many diseases and disease risks including CJD. TBI does not believe the FDA has sufficiently demonstrated (quantitatively or scientifically) relevant risk for expanding its oversight to include other diseases in addition to HIV and hepatitis. As previously expressed, the application of "relevant" is subject to FDA's sole determination which is further complicated by the FDA's interpretation of the terms "sufficiently prevalent", "'risk" and "appropriate screening". These terms are not sufficiently defined. Additionally, relevant risk is broadly applied and does not sufficiently address risk by specific tissue that TBI will comment on in the following subtitle.

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY (TSE) AND CREUTZFELDT-JACOB DISEASE **(CJD):** The FDA seems to be particularly concerned about the transmission of CJD through dura mater and cornea transplants. Yet, apparently based on these reports, the FDA proposes to apply the screening to all tissue. Of particular concern to TBI is if the FDA would require the tissue and eye banking community to screen for and reject donors who exhibit changes in speech and gait. Changes in speech and gait are symptoms that might apply to many medically suitable donors most likely not associated with TSE / CJD.

TBI would like to stress that the reports of the transmissions of disease for both dura mater and cornea1 tissue occurred outside of the United States except for one reported case of CJD via cornea transplant in the U.S. The cornea is this case was never evaluated or screened by the local eye bank and occurred before the promulgation of any organized screening standards.

TBI is working with the Eye Bank Association of America to review the adequacy of the screening of eye donors for CJD. Walter Stark, M.D., head of the Cornea Service at the Wilmer Eye Institute at Johns Hopkins University Medical Center and TBI's National Medical Director is participating with Richard Johnson, M.D., also from Johns Hopkins and author of many publications on prion disease along with others on a special ad hoc committee investigating this issue. TBI recommends the FDA take no action regarding the screening for TSE / CJD until further evaluation by this EBAA ad hoc committee can be completed and the results can be shared with the FDA.

TBI knows of no currently available method to test for TSE except for a brain biopsy. TBI agrees with the FDA that testing for TSE through a brain biopsy is not feasible because the test results would not be available before cornea1 tissue is optimally utilized for transplantation. This would not be in the best interest of the

patient receiving the cornea. There is also a significant question on the impact upon the rate of cornea1 donation if consent for a brain autopsy was also needed. A reduction in donors and a return to waiting lists is also not in the best interest of the patient or patient outcomes.

LEGISLATIVE CONSENT: TBI disagrees with the FDA's contention that requiring a donor medical history interview for corneas obtained under legislative consent is necessary to ensure the risk of communicable disease transmission is appropriately assessed. TBI believes the medical/social history screening of cases obtained under legislative consent statutes to be every bit as comprehensive, and in some cases more so, than cases obtained with next-of-kin consent and a medical/social history questionnaire. In June of 1998, nearly five years after the FDA's interim final rule was published, the EBAA's Policy and Position Research Committee concluded there is no medical or scientific evidence to indicate there is any increased risk of communicable disease transmission from cornea1 tissue obtained legislative consent. TBI has twenty-five years of experience with both legislative consent and next-of-kin consent programs. Our organizational experience is consistent with the conclusions of the aforementioned EBAA report.

The removal of the exemption from the requirement for a donor medical history interview for corneas obtained under legislative consent would effectively eliminate these very effective programs. Not only would the quantity of cornea1 tissue be critically affected but also the quality of cornea1 tissue would be diminished to the detriment of the patients, surgeons and hospitals in the affected communities.

The only alternative that would allow the proposed rule and State laws on legislative consent to co-exist would be to allow the medical examiner or pathologist who performs the autopsy to qualify as an "individual knowledgeable about the donor's medical history and relevant social behavior". Additionally, the medical examiner or pathologist must be allowed to respond to a modified set of history questions appropriate to their medical examination. Other medical and social history can be obtained through the case file containing investigators' reports, hospital charts or other sources of donor history.

The removal of the exception from the requirement for a donor medical history interview for corneas obtained under legislative consent in the proposed rule seems to be prompted by FDA's concerns about TSE / CJD. Enclosed is a table summarizing data from the Office of the Chief Medical Examiner in the State of Maryland and data from the Medical Eye Bank of Maryland for 1998. Our findings indicate that TSE / CJD cases are not cases brought to the medical examiner's office for determination of the cause of death. There were no such cases in 1998 nor could the Chief Medical Examiner ever recall a TSE / CJD case brought in for autopsy. Furthermore, if any such case were to be brought into the medical

examiner's office, it would be handled under a "highly infectious" protocol and would be off limits to the tissue and eye bank staff.

CONFIRMATORY TESTING: TBI urges the FDA to be more consistent in its approach to donor testing, in particular, confirmatory testing. In § 127 1.80 (c) the FDA proposes that testing be performed using appropriate FDA-licensed, approved or cleared donor screening tests in accordance with the manufacturers instructions. However, in § 1271.80 (d)(l) there is no exception for hepatitis B. FDA approved tests for hepatitis B recognize the validity of confirmatory testing in the manufacturer's instructions.

COLLECTION OF BLOOD SAMPLES: TBI believes the FDA's proposal to define an adequate blood sample for testing is contradictory. At one point, it is proposed blood samples be drawn at the time of tissue recovery or within 48 hours after recovery. This eliminates the ability to use pre transfusion samples thereby eliminating many donors, At another point, the use of blood drawn before tissue recovery is proposed by allowing testing of a sample drawn after blood loss but before infusion/transfusion TBI believes it is critical for the FDA to make no change to the regulation currently in place under the "tissue final rule". To do otherwise would eliminate a significant number of tissue and eye donors.

ESTABLISHMENTS NOT REQUIRED TO COMPLY: In §1271.20(d), FDA would exclude from registration "establishments that only receive or store human cellular or tissue based products solely for pending scheduled implantation, transplantation, infusion or transfer within the same facility." TBI presumes this is intended to exempt hospitals, ASCs or similar organizations that utilize the allografts provided by the tissue and eye banking community. Please be advised that a great many hospitals and other surgical facilities obtain tissue allografts for stock without having a specific patient already scheduled for surgery. The key word is "scheduled" which TBI suggests should be deleted from the final registration rule otherwise the proposed regulation would apply to most of the hospitals in the United States.

FDA ECONOMIC IMPACT ESTIMATES: The FDA's estimated economic impact of the proposed regulations is significantly understated. The agency states the areas likely to be affected are donor screening, donor testing, record keeping, quarantine, donor suitability determinations, donor documentation, allograft documentation, labeling and record keeping.

The FDA only estimated the time needed for one person to "compare the proposed regulations against the facility's current standards". If implemented in their current

form, the proposed regulations would necessitate changes for every one of the operational functions identified by the FDA (listed above) and others not identified for every eye bank in the United States, The time and resources necessary to comply would not be limited to "comparing" or identifying items for compliance.

For example, any identified area for change after comparing the FDA regulations to an eye bank facility's operating standards is just the first step. Typically, management and an eye bank's Medical Director must provide oversight, direction and approval of any change. Corrective action must be promulgated. Changes in the eye bank facility's standard operating procedures must be made and implemented. Most likely forms and/or logs must be changed. The most significant amount of time and resources is related to the retraining of all affected staff and subsequent quality assurance to insure compliance.

The economic impact is certainly more than the FDA's estimated $45 to $229. TBI estimates the annual impact at $10,000 to $20,000 per average tissue and eye bank. If hospitals that store allograft tissue for unscheduled surgery are affected the overall impact is much greater still. TBI urges the FDA to revise the economic impact of the regulation.

Tissue Banks International is a non-profit organization of eye and tissue banks located throughout the United States. TBI has 31 locations and operates in 14 states and the District of Columbia. Some TBI banks have been operating for over 50 years providing cornea1 and other ocular tissues to help restore vision, musculoskeletal tissue for bone grafts and muscle repair, skin for burn victims, heart valves to repair congenital heart defects and many more tissues and medical applications.

TBI would be pleased to discuss with the FDA any of our comments.

Sincerely,

Richard L. Fuller /sjc

Richard L. Fuller
President/CEO
Tissue Banks International

OFFICE OF THE CHIEF MEDICAL EXAMINER (MEO)
Baltimore, Maryland
1998 Statistics for the State of Maryland

The following is an analysis of the total caseload of the Chief Medical Examiner of the State of Maryland for the year 1998.

	Reported	Autopsied
Total Cases Reported:	8003	
Total Cases Autopsied:		3184
*Total cases Nervous System Diseases (NSD):	43 (0.5%)	
Total NSD cases autopsied:		4 (0.1%)
Total # of Eye Donors from NSD cases:	0 (0%)	0 (0%)

Total CJD Cases:

Reported to MEO :	0
Autopsied by MEO:	0
Cornea Donors to Eye Bank:	0

*Where a CJD case would be classified per MEO

Discussion:

- The scientific literature indicates one case of CJD per million in general population
- The 1998 population of the State of Maryland is 5.1 million thus; it could be expected that five cases CJD cases might occur in one year. (1988)
- The total number of deaths (all causes) in Maryland is approximately 40,000 annually (I 998 data) thus; it could be expected that one case might be a MEO case in one year (1998) (MEO cases equal 20% of total annual deaths) if MEO cases were representative of the general population (of deaths).
- MEO cases are a distinct sub set of the general death population primarily including accident, suicide and homicide

CJD cases are generally not reported to MEO
CJD cases are generally not autopsied by MEO
CJD cases (as an infectious disease case) would not be available to the eye bank by definition
CJD cases would be screened out under current medical standards as would any other case with unknown neurological disorders.

SUMMARY

The likelihood of a potential CJD case being made available to the eye bank by the MEO is nil by definition and category as determined by the MEO. The likelihood of the eye bank recovering tissue from a MEO CJD case is nil because by definition unknown nervous system disorders are ruled out.

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